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(72) KOTHRADÉ, Stephan, DE  
(72) ERNST, Andreas, DE  
(72) SANNER, Axel, DE  
(71) BASF AKTIENGESELLSCHAFT, DE  
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(54) **PRODUCTION DE FORMES DE DOSAGE SOLIDES**  
(54) **THE PRODUCTION OF SOLID DOSAGE FORMS**

(57) Solid dosage forms are produced by mixing and melting at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives, extruding the mixture and shaping, wherein homo- and/or copolymers of 2-substituted oxazolines are used as polymeric binder.

The production of solid dosage forms

The invention relates to a process for producing solid dosage  
5 forms by mixing at least one polymeric binder and, where  
appropriate, at least one active ingredient and, where  
appropriate, conventional additives to form a plastic mixture,  
and shaping. The invention particularly relates to a process for  
producing solid pharmaceutical forms.

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Classical processes for producing solid pharmaceutical forms,  
especially tablets, are carried out batchwise and comprise a  
plurality of stages. Pharmaceutical granules represent an  
important intermediate therefor. Thus, for example, it is  
15 disclosed in the book "Pharmazeutische Technologie", authors  
Prof. Bauer, Frömmig and Führer, Thieme Verlag, pages 292 et  
seq., that drug forms can be obtained from the melts by dry  
granulation. The possibility of producing solidified melt  
granules either by melting and shock solidification, by casting  
20 and comminuting or by prilling in spray towers is described. One  
problem with these processes is the accurate shaping which is  
necessary for producing drugs. Irregular particles or fragments  
are frequently produced so that the resulting shape by no means  
corresponds to customary drug forms, and granules therefore have  
25 only little importance as a drug form on their own. Production of  
desired solid drug forms requires the use of further process  
steps such as compression in tableting machines. This is  
time-consuming and costly.

30 A considerably simpler continuous process for producing solid  
pharmaceutical forms has been known for some time and entails  
extruding a solvent-free melt of a polymeric binder containing  
active ingredients, and shaping this extrudate to the required  
drug form, for example in a calender with molding rolls, see  
35 EP-A-240 904, EP-A-240 906 and EP-A-337 256 and EP-A-358105. It  
is possible in this way to achieve specific shaping. The  
polymeric binders employed are, in particular, polymers of  
N-vinylpyrrolidone or copolymers thereof, eg. with vinyl acetate.

40 The use of polyoxazolines in various sectors, for example as  
binders in pharmaceutical preparations, is known. WO 95/01383,  
WO 95/01384, WO 95/06078 and WO 95/06079 disclose water- or  
alcohol-soluble or dispersible elastomeric copolymers which  
contain from 10 to 60% by weight of polyoxazolines with a degree  
45 of polymerization of from 10 to 2000 as building block. The  
copolymers can be used for hair care compositions and drugs for  
topical administration.

Investigations on polyoxazolines for their clearance and biodistribution (Zalipsky et al., J. Pharm. Sci., 85, (1996), 133), toxicity (Kobayashi et al., Macromol. Chem. 184, (1983), 5 793) and pharmacokinetic properties (Goddard et al., J. Contr. Rel. 10, (1989) 5) have been carried out and revealed that polyoxazolines can be used to produce liposomes and as carrier polymers for pharmaceutical active ingredients.

- 10 US-A-5 410 016 describes hydrogels from polymerized and crosslinked macromers which contain hydrophilic oligomers, eg. polyoxazolines, with biodegradable portions for use as drug carriers for drug forms with controlled release for time-limited protection of tissues, to prevent adhesions after surgical  
15 operations and the like.

WO 94/03544 describes protein-compatible polymer blends of water-soluble polymers and matrix polymers and their use as stable hydrophilic surfaces in vessels for storing protein  
20 solutions. Poly(ethyloxazoline) is also suitable as water-soluble polymer.

WO 93/16687 discloses water-soluble macromers (prepolymers) which have been modified with at least two substituents capable of  
25 free-radical polymerization. Suitable macromers include poly(ethyloxazolines). The macromers are subjected to a photopolymerization in order to encapsulate biological materials with gel formation.

- 30 US-A-5 536 505 discloses a matrix system which comprises a homogeneous mixture of poly(2-ethyl-2-oxazoline), cellulose acetate with a degree of substitution of about 0.5 to 3.0 and a water-soluble active ingredient. The matrix system permits controlled release of active ingredients.

35 The use of poly(ethyloxazoline) and poly(methacrylic acid) or poly(acrylic acid) for forming polymer complexes whose solubility in water can be controlled by an electric current as system for pulsed release of active ingredient is described by Kwon et al.,  
40 Proc. 19th Int. Symp. Contr. Rel. Bioact. Mater. (1992) 243 and Kwon et al., Nature, 354 (1991) 291, and Bae et al., in "Polymeric Drugs and Drug Administration", ACS Symp. Ser. 545, (1994) 98.

45 WO 94/20073 discloses lipid-polymer conjugates in which a vesicle-forming lipid is covalently connected to a water- and solvent-soluble polymer in order to increase the half-life of

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liposomes in the bloodstream. Polyoxazolines are among the water- and solvent-soluble polymers which can be used.

WO 92/06678 describes biocompatible microcapsules which can be used for implanting exogenous material, the microcapsules having an outer layer of a water-soluble nonionic polymer such as poly(ethylene oxide) to prevent cells adhering to the surface of the microcapsules. Also suitable in place of poly(ethylene oxide) are other water-soluble polymers such as poly(ethyloxazoline).

Shenouda et al., Int. J. Pharmac., 61 (1990) 127 describe the partial coating of hydroxypropylmethylcellulose capsules with polyoxazolines for release of active ingredients from the capsules at a constant rate. The use of a matrix of hydroxypropylmethylcellulose and poly(ethyloxazoline) do not result in these release characteristics.

Chun et al., Proc. 23rd Int. Symp. Contr. Rel. Bioact. Mater. (1996) 343 describe influencing the shape and size of alginate microspheres by introducing or coating with various substances including poly(ethyloxazoline), and the effect thereof on the release of active ingredients. Alginate microspheres with added polymer were smaller than microspheres of pure alginate.

However, the production of these dosage forms such as microcapsules and microparticles, and the introduction of the active ingredient, are very complicated and thus time-consuming and costly.

It is an object of the present invention to provide a simple and low-cost process for producing solid dosage forms, especially drug forms.

We have found that this object is achieved by producing the dosage forms by converting the binder into the plastic state, in particular by melt extrusion, with use of polyoxazolines as binders.

The present invention therefore relates to a process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, and shaping, wherein homo- and/or copolymers of 2-substituted oxazolines are used as polymeric binder.

The terms detailed below have the following meanings for the purpose of the present invention:

Alkyl is straight-chain or branched alkyl generally having 1 to 30 carbon atoms, preferably C<sub>1</sub>-C<sub>21</sub>-alkyl and, in particular, C<sub>1</sub>-C<sub>6</sub>-alkyl. Examples of alkyl groups are methyl, ethyl, n-propyl, 5 isopropyl, n-butyl, n-hexyl, 2-ethylhexyl, n-nonyl, n-dodecyl, cetyl and stearyl.

Alkenyl is straight-chain or branched alkenyl having 3 to 20, in particular 3 to 8, carbon atoms. Examples are hexenyl and oleyl.

10 Aryl is preferably phenyl or naphthyl.

Acyl is preferably -COH or COC<sub>1</sub>-C<sub>18</sub>-alkyl, in particular COC<sub>1</sub>-C<sub>6</sub>-alkyl.

15 Heterocyclyl is an aromatic or nonaromatic group having 5 or 6 ring atoms with 1, 2 or 3 heteroatoms which are selected, independently of one another, from O, S and N. Examples of aromatic heterocyclic groups are pyrrolyl, imidazolyl, thiazolyl, 20 triazolyl, furyl, thienyl, oxazolyl, isoxazolyl, pyridyl and pyrimidinyl. Examples of nonaromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuryl, morpholinyl, piperidinyl and piperazinyl.

25 The novel process makes it possible to produce solid dosage forms in a simple and low-cost manner. The advantageous properties of the polyoxazolines are not impaired by conversion into the plastic state.

30 Dosage forms mean herein all forms which are suitable for use as drugs, plant treatment compositions, human and animal foods and for delivering fragrances and perfume oils. These include, for example, tablets of any shape, pellets, granules, but also larger forms such as cubes, blocks (bricks) or cylindrical forms, which 35 can be used, in particular, as human or animal foods.

The dosage forms obtainable according to the invention generally comprise:

- 40 a) 0-99% by weight, in particular 0.1-60% by weight (based on the total weight of the dosage form) of an active ingredient,
- b) 1-100% by weight, in particular 40-99.9% by weight of a polymeric binder and
- 45 c) where appropriate additives.

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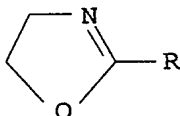
If the dosage form is employed for human or animal food purposes, the active ingredient may be absent, ie. the dosage form may comprise up to 100% of the polymeric binder.

- 5 The polymeric binders used according to the invention are oxazoline homopolymers and/or copolymers of various oxazolines or oxazolines and other monomers (comonomers). The copolymers preferably contain at least 10% by weight, in particular at least 20% by weight and, particularly preferably, at least 50% by weight of oxazoline units. Examples of suitable comonomers are monoethylenically unsaturated carboxylic acids such as acrylic acid or methacrylic acid.

The copolymerization of oxazolines is described, for example, in 15 US 4,016,192.

The polymers used according to the invention preferably comprise oxazoline units of the formula

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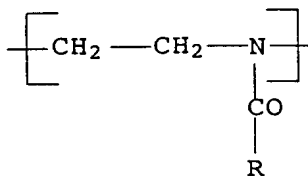
- where R is alkyl which may be interrupted by one or more oxygen atoms (between which there are at least 2 carbon atoms) or alkenyl, aryl, cycloalkyl or heterocyclyl, where R may have 1, 2 or 3 substituents which are selected, independently of one another, from alkyl, halogen, OH, alkoxy, acyl, acyloxy, COR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, amino, monoalkylamino, dialkylamino, nitro, aryl or heterocyclyl, where R<sup>1</sup> is OH, OC<sub>1</sub>-C<sub>6</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1</sub>-C<sub>6</sub>-alkyl or N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub>, or the abovementioned substituents which are, however, linked to the oxazoline ring via O, S, NR<sup>2</sup>, P(OR<sup>2</sup>)<sub>2</sub>, 30 SiOR<sup>3</sup>, Si(R<sup>3</sup>)<sub>3</sub>, where R<sup>2</sup> is H or C<sub>1</sub>-C<sub>6</sub>-alkyl, and the R<sup>3</sup> radicals are, independently of one another, C<sub>1</sub>-C<sub>6</sub>-alkyl.

- R is preferably alkyl and hydroxyalkyl having 1 to 30, in particular 1 to 21, carbon atoms. R is particularly preferably 40 methyl, ethyl, hydroxyethyl, hydroxypropyl, stearyl or cetyl.

A review of the synthesis of oxazolines and the polymerization thereof is to be found in Henkel-Referata 28/1992, 43-47.

- 45 The polyoxyazolines are obtained in a manner known per se by cationic ring-opening polymerization to form units of the formula

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In the chemical structure, the polyoxazolines used according to  
10 the invention as binders are N-acylated polyethyleneimines. They  
can be converted by hydrolysis, with elimination of the acyl  
group, into polyethyleneimines which are distinguished, by  
comparison with polymers obtained by polymerization of  
15 ethyleneimine, by a high degree of linearity. The degree of  
polymerization of polyoxazolines can be adjusted virtually as  
desired via the amount of catalyst employed. The preparation is  
normally carried out as solution or bulk polymerization with  
trifluoromethanesulfonic ester or methyl para-toluenesulfonate or  
other known catalysts suitable for cationic polymerization.

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The copolymers can be prepared by, on the one hand,  
copolymerizing various oxazolines and, on the other hand,  
copolymerizing oxazolines with other suitable monomers with  
sufficiently high nucleophilicity.

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Besides the polymeric binders described above, it is possible to  
employ in particular up to 30% by weight, based on the total  
weight of the binder, of other binders such as polymers,  
copolymers, cellulose derivatives and starch. Suitable examples  
30 are:

Polyvinylpyrrolidone (PVP), copolymers of N-vinylpyrrolidone  
(NVP) and vinyl esters, especially vinyl acetate, copolymers of  
vinyl acetate and crotonic acid, partially hydrolyzed polyvinyl  
35 acetate, polyvinyl alcohol, poly(hydroxyalkyl acrylates),  
poly(hydroxyalkyl methacrylates), polyacrylates and  
polymethacrylates (Eudragit types), copolymers of methyl  
methacrylate and acrylic acid, polyacrylamides, polyethylene  
glycols, polyvinyl formamide (partially or completely hydrolyzed  
40 where appropriate), cellulose esters, cellulose ethers,  
especially methyl cellulose and ethyl cellulose,  
hydroxyalkylcelluloses, especially hydroxypropylcellulose,  
hydroxyalkylalkylcelluloses, especially  
hydroxypropylethylcellulose, cellulose phthalates, especially  
45 cellulose acetate phthalate and hydroxypropylmethylcellulose  
phthalate, and mannans, especially galactomannans. Of these,  
polyvinylpyrrolidone, copolymers of N-vinylpyrrolidone and vinyl

esters, poly(hydroxyalkyl acrylates), poly(hydroxyalkyl methacrylates), polyacrylates, polymethacrylates, alkylcelluloses and hydroxyalkylcelluloses are particularly preferred.

- 5 The polymeric binder must soften or melt in the complete mixture of all the components in the range of from 50 to 200°C, preferably 60 to 130°C. The glass transition temperature of the mixture must therefore be below 200°C, preferably below 130°C. If necessary, it is reduced by conventional pharmacologically acceptable
- 10 plasticizing auxiliaries. The amount of plasticizer does not exceed 30% of the total weight of binder and plasticizer in order to form storage-stable drug forms which show no cold flow. However, the mixture preferably contains no plasticizer.

- 15 Examples of such plasticizers are:

Long-chain alcohols, ethylene glycol, propylene glycol, glycerol, trimethylolpropane, triethylene glycol, butanediols, pentanols such as pentaerythritol, hexanols, polyethylene glycols,

20 polypropylene glycols, polyethylene/propylene glycols, silicones, aromatic carboxylic esters (eg. dialkyl phthalates, trimellitic esters, benzoic esters, terephthalic esters) or aliphatic dicarboxylic esters (eg. dialkyl adipates, sebacic esters, azelaic esters, citric and tartaric esters), fatty acid esters

25 such as glycerol mono-, di- or triacetate or sodium diethyl sulfosuccinate. The concentration of plasticizer is generally from 0.5 to 15, preferably 0.5 to 5, % of the total weight of the mixture.

- 30 Conventional pharmaceutical auxiliaries, whose total amount can be up to 100% of the weight of the polymer, are, for example, extenders and bulking agents such as silicates or diatomaceous earth, magnesium oxide, aluminum oxide, titanium oxide, stearic acid or its salts, eg. the magnesium or calcium salt,

- 35 methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal or cornstarch, potato flour, polyvinyl alcohol, in particular in a concentration of from 0.02 to 50, preferably 0.20 to 20, % of the total weight of the mixture.

- 40 Lubricants such as aluminum and calcium stearates, talc and silicones, in a concentration of from 0.1 to 5, preferably 0.1 to 3, % of the total weight of the mixture.

- Flowability agents such as animal or vegetable fats, especially
- 45 in hydrogenated form and those which are solid at room temperature. These fats preferably have a melting point of 50°C or above. Triglycerides of C<sub>12</sub>, C<sub>14</sub>, C<sub>16</sub> and C<sub>18</sub> fatty acids are



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preferred. It is also possible to use waxes such as carnauba wax. These fats and waxes may be admixed advantageously alone or together with mono- and/or diglycerides or phosphatides, especially lecithin. The mono- and diglycerides are preferably  
5 derived from the abovementioned fatty acid types. The total amount of fats, waxes, mono-, diglycerides and/or lecithin is from 0.1 to 30, preferably 0.1 to 5, % of the total weight of the composition for each layer.

10 Dyes, such as azodyes, organic or inorganic pigments or dyes of natural origin, with preference for inorganic pigments in a concentration of from 0.001 to 10, preferably 0.5 to 3, % of the total weight of the mixture.

15 Stabilizers such as antioxidants, light stabilizers, hydroperoxide destroyers, radical scavengers, stabilizers against microbial attack.

It is also possible to add wetting agents, preservatives,  
20 disintegrants, adsorbents, release agents and propellants (cf., for example, H. Sucker et al., Pharmazeutische Technologie, Thieme-Verlag, Stuttgart 1978).

Auxiliaries include for the purpose of the invention substances  
25 for producing a solid solution of the active ingredient. Examples of these auxiliaries are pentaerythritol and pentaerythritol tetraacetate, polymers such as polyethylene oxides and polypropylene oxides and their block copolymers (poloxamers), phosphatides such as lecithin, homo- and copolymers of  
30 vinylpyrrolidone, surfactants such as polyoxyethylene  
40 stearate, and citric and succinic acids, bile acids, sterols and others as indicated, for example, in J. L. Ford, Pharm. Acta Helv. 61 (1986) 69-88.

35 Auxiliaries are also regarded as being bases and acids added to control the solubility of an active ingredient (see, for example, K. Thoma et al., Pharm. Ind. 51 (1989) 98-101).

The only precondition for the suitability of auxiliaries is  
40 adequate thermal stability.

Active ingredients mean for the purpose of the invention all substances with a physiological effect as long as they do not decompose under the processing conditions. These are, in  
45 particular, pharmaceutical active ingredients (for humans and animals), active ingredients for plant treatment, insecticides, active ingredients of human and animal foods, fragrances and

perfume oils. The amount of active ingredient per dose unit and the concentration may vary within wide limits depending on the activity and the release rate. The only condition is that they suffice to achieve the desired effect. Thus, the concentration of  
5 active ingredient can be in the range from 0.1 to 95, preferably from 20 to 80, in particular 30 to 70, % by weight. It is also possible to employ combinations of active ingredients. Active ingredients for the purpose of the invention also include vitamins and minerals. The vitamins include the vitamins of the A  
10 group, the B group, by which are meant besides B<sub>1</sub>, B<sub>2</sub>, B<sub>6</sub> and B<sub>12</sub> and nicotinic acid and nicotinamide also compounds with vitamin B properties such as adenine, choline, pantothenic acid, biotin, adenylic acid, folic acid, orotic acid, pangamic acid, carnitine, p-aminobenzoic acid, myo-inositol and lipoic acid, and vitamin C,  
15 vitamins of the D group, E group, F group, H group, I and J groups, K group and P group. Active ingredients for the purpose of the invention also include therapeutic peptides. Plant treatment agents include, for example, vinclozolin, epoxiconazole and quinmerac.

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The novel process is suitable, for example, for processing the following active ingredients:

acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir,  
25 alprazolam, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclomethasone, benserazide, benzalkonium hydrochloride, benzocaine, benzoic acid, betamethasone,  
30 bezafibrate, biotin, biperiden, bisoprolol, bromazepam, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, cefachlor, cefalexin, cefadroxil, cefazoline, cefixime, cefotaxime, ceftazidime, ceftriaxone,  
35 cefuroxime, selegiline, chloramphenicol, chlorhexidine, chlorpheniramine, chlortalidone, choline, cyclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, codeine, cholestyramine, cromoglycic  
40 acid, cyanocobalamin, cyproterone, desogestrel, dexamethasone, dexpanthenol, dextromethorphan, dextropropoxiphen, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, dihydroergotoxin, diltiazem, diphenhydramine, dipyrindamole, dipyrone, disopyramide, domperidone, dopamine, doxycycline,  
45 enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus globulus, famotidine, felodipine, fenofibrate, fenoterol,

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- fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gallopamil, gemfibrozil, gentamicin, Gingko biloba, glibenclamide, glipizide, clozapine, Glycyrrhiza glabra, griseofulvin, guaifenesin,
- 5 haloperidol, heparin, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphone, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, iohexol, iopamidol, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labetalol,
- 10 lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, imipramine, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, methyl dopa, methylprednisolone, metoclopramide, metoprolol, miconazole,
- 15 midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamin mixtures or combinations and mineral salts, N-methylephedrine, naftidrofuryl, naproxen, neomycin, nifedipine, nimodipine, nitrazepam, nitrendipine, nizatidine,
- 20 norethisterone, norfloxacin, norgestrel, nortriptyline, nystatin, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, pentoxifylline, phenoxymethylpenicillin, phenylephrine, phenylpropanolamine, phenytoin, piroxicam,
- 25 polymyxin B, povidone-iodine, pravastatin, prazepam, prazosin, prednisolone, prednisone, bromocriptine, propafenone, propranolol, proxyphylline, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin,
- 30 salicylic acid, simvastatin, somatropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulfasalazine, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, tetracycline, theophylline, thiamine, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide,
- 35 triamterene, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, folic acid, zidovudine.

- Preferred active ingredients are ibuprofen (as racemate, enantiomer or enriched enantiomer), ketoprofen, flurbiprofen,
- 40 acetylsalicylic acid, verapamil, paracetamol, nifedipine or captopril.

- The novel dosage forms are particularly suitable, because of the relatively low glass transition temperature of from 60 to 80°C for
- 45 the polyoxazolines used according to the invention as binders, for thermally sensitive active ingredients. These include, for example, enzymes such as pancreatin, lipases ...

The novel process is also advantageous for producing solid dosage forms for thermally sensitive crop protection agents.

- 5 To produce the solid dosage forms, a plastic mixture of the components (melt) is prepared and then subjected to a shaping step. There are various ways of mixing the components and forming the melt. The mixing can take place before, during and/or after the formation of the melt. For example, the components can be  
10 mixed first and then melted or be mixed and melted simultaneously. The plastic mixture is often then homogenized in order to disperse the active ingredient thoroughly.

- However, it has proven preferable, especially when sensitive  
15 active ingredients are used, first to melt the polymeric binder and, where appropriate, make a premix with conventional pharmaceutical additives, and then to mix in (homogenize) the sensitive active ingredient(s) in the plastic phase in intensive mixers with very short residence times. The active ingredient(s)  
20 can for this purpose be employed in solid form or in solution or dispersion.

- The components are generally employed as such in the production process. However, they can also be used in liquid form, ie. as  
25 solution, suspension or dispersion.

- Suitable solvents for the liquid form of the components are primarily water or a water-miscible organic solvent or a mixture thereof with water. However, it is also possible to use organic  
30 solvents which are immiscible or miscible with water. Suitable water-miscible solvents are, in particular, C<sub>1</sub>-C<sub>4</sub>-alkanols such as ethanol, isopropanol or n-propanol, polyols such as ethylene glycol, glycerol and polyethylene glycols. Suitable water-immiscible solvents are alkanes such as pentane or hexane,  
35 esters such as ethyl acetate or butyl acetate, chlorinated hydrocarbons such as methylene chloride, and aromatic hydrocarbons such as toluene and xylene. Another solvent which can be used is liquid CO<sub>2</sub>.

- 40 The solvent used in the individual case depends on the component to be taken up and the properties thereof. For example, pharmaceutical active ingredients are frequently used in the form of a salt which is, in general, soluble in water. Water-soluble active ingredients can therefore be employed as aqueous solution  
45 or, preferably, be taken up in the aqueous solution or dispersion of the binder. A corresponding statement applies to active ingredients which are soluble in one of the solvents mentioned,

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if the liquid form of the components used is based on an organic solvent.

It is possible where appropriate to replace melting by  
5 dissolving, suspending, or dispersing in the abovementioned  
solvents, if desired and/or necessary with the addition of  
suitable auxiliaries such as emulsifiers. The solvent is then  
generally removed to form the melt in a suitable apparatus, eg.  
an extruder. This will be comprised by the term mixing  
10 hereinafter.

The melting and/or mixing takes place in an apparatus customary  
for this purpose. Particularly suitable ones are extruders or  
containers which can be heated where appropriate and have an  
15 agitator, eg. kneaders (like those of the type to be mentioned  
below).

A particularly suitable mixing apparatus is one employed for  
mixing in plastics technology. Suitable apparatuses are  
20 described, for example, in "Mischen beim Herstellen und  
Verarbeiten von Kunststoffen", H. Pahl, VDI-Verlag, 1986.  
Particularly suitable mixing apparatuses are extruders and  
dynamic and static mixers, and stirred vessels, single-shaft  
stirrers with stripper mechanisms, especially paste mixers,  
25 multishaft stirrers, especially PDSM mixers, solids mixers and,  
preferably, mixer/kneader reactors (eg. ORP, CRP, AP, DTB  
supplied by List or Reactotherm supplied by Krauss-Maffei or  
Ko-Kneter supplied by Buss), trough mixers and internal mixers or  
rotor/stator systems (eg. Dispax supplied by IKA).

30 In the case of sensitive active ingredients it is preferable  
first for the polymeric binder to be melted in an extruder and  
then for the active ingredient to be admixed in a mixer/kneader  
reactor. On the other hand, with less sensitive active  
35 ingredients, a rotor/stator system can be employed for vigorously  
dispersing the active ingredient.

The mixing apparatus is charged continuously or batchwise,  
depending on its design, in a conventional way. Powdered  
40 components can be introduced in a free feed, eg. via a weigh  
feeder. Plastic compositions can be fed in directly from an  
extruder or via a gear pump, which is particularly advantageous  
if the viscosities and pressures are high. Liquid media can be  
metered in by a suitable pump unit.

45 The mixture obtained by mixing and/or melting the binder, the  
active ingredient and, where appropriate, the additive(s) ranges

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from pasty to viscous (plastic) or fluid and is therefore extrudable. The glass transition temperature of the mixture is below the decomposition temperature of all the components present in the mixture. The binder should preferably be soluble or  
5 swellable in a physiological medium.

The steps of mixing and melting in the process can be carried out in the same apparatus or in two or more separately operating apparatuses. The preparation of a premix can take place in one of  
10 the conventional mixing apparatuses described above. A premix of this type can then be fed directly, for example, into an extruder and subsequently extruded, where appropriate with the addition of other components.

15 It is possible in the novel process to employ as extruders single screw machines, intermeshing screw machines or else multiscrew extruders, especially twin screw extruders, corotating or counterrotating and, where appropriate, equipped with kneading disks. If it is necessary in the extrusion to evaporate a  
20 solvent, the extruders are generally equipped with an evaporating section. Particularly preferred extruders are those of the ZKS series from Werner & Pfleiderer.

It is also possible according to the invention to produce  
25 multilayer pharmaceutical forms by coextrusion, in which case a plurality of mixtures of the components described above is fed together to an extrusion die so as to result in the required layered structure of the multilayer pharmaceutical form. It is preferable to use different binders for different layers.

30 Multilayer drug forms preferably comprise two or three layers. They may be in open or closed form, in particular as open or closed multilayer tablets.

35 At least one of the layers contains at least one pharmaceutical active ingredient. It is also possible for another active ingredient to be present in another layer. This has the advantage that two mutually incompatible active ingredients can be processed or that the release characteristics of the active  
40 ingredient can be controlled.

The shaping takes place by coextrusion with the mixtures from the individual extruders or other units being fed into a common coextrusion die and extruded. The shape of the coextrusion die  
45 depends on the required pharmaceutical form. Examples of suitable dies are those with a flat orifice, called a slit die, and dies with an annular orifice. The design of the die depends on the

polymeric binder used and the required pharmaceutical form.

The resulting mixture is preferably solvent-free, ie. it contains neither water nor an organic solvent.

5

The plastic mixture is, as a rule, subjected to final shaping. This can result in a large number of shapes depending on the die and mode of shaping. For example, if an extruder is used, the extrudate can be shaped between a belt and a roll, between two  
10 belts or between two rolls, as described in EP-A-358 105, or by calendering in a calender with two molding rolls, see, for example, EP-A-240 904. Other shapes can be obtained by extrusion and hot- or cold-cut of the extrudate, for example small-particle and uniformly shaped pellets. Hot-cut pelletization usually  
15 results in lenticular dosage forms (tablets) with a diameter of from 1 to 10 mm, while strip pelletization normally results in cylindrical products with a length to diameter ratio of from 1 to 10 and a diameter of from 0.5 to 10 mm. It is thus possible to produce monolayer but also, on use of coextrusion, open or closed  
20 multilayer dosage forms, for example oblong tablets, coated tablets, pastilles and pellets. The resulting granules can also be ground to a powder and compressed to tablets in a conventional way. Micropastilles can be produced by the Rotoform-Sandvik process. These dosage forms can be rounded and/or provided with a  
25 coating by conventional methods in a subsequent process step. Examples of materials suitable for film coatings are polyacrylates such as the Eudragit types, cellulose esters such as the hydroxypropylcellulose phthalates, and cellulose ethers, such as ethylcellulose, hydroxypropylmethylcellulose or  
30 hydroxypropylcellulose.

In specific cases there may be formation of solid solutions. The term solid solutions is familiar to the skilled worker, for example from the literature cited at the outset. In solid  
35 solutions of active ingredients in polymers, the active ingredient is in the form of a molecular dispersion in the polymer.

The following examples are intended to illustrate the novel  
40 process without restricting it, however.

#### Examples

To produce the solid dosage forms, the stated amounts of crop  
45 protection agent or drug, polymeric binder (polyethyloxazoline;  $M_w \sim 400,000$ ), nonionic surfactant and ionic dispersant are introduced, either mixed or separately, into a corotating,

## 15

closely intermeshing twin screw extruder (Werner und Pfleiderer ZSK 30) and extruded through 12 temperature zones. The speed of the screws was varied in the range from 100 to 300 rpm, and the temperature was in the range from 30 to 80°C in the feed sections 5 and 80 to 160°C in the plasticizing sections. The exact conditions are indicated in the individual examples. The output was 2 to 4 kg per hour and the residence time was 1 to 2 minutes. The active ingredient, the polymer and the additives were fed via weigh feeders to the extruder inlet and were melted. The nonionic 10 surfactant was, where appropriate, then fed in as liquid and incorporated with mixing and kneading elements. If required, the melt was degassed before the addition. The melt discharged from the extruder through a die was, after cooling, crushed, ground and graded by screening. The 400 to 500 µm screen fraction was 15 used for the use tests. The conditions are summarized in the following Table 1.

Table 1:

20	Example No.	Active ingredient % by wt	Poly-ethyloxazoline % by wt	Lutensol AT 25 <sup>a)</sup> % by wt	Addition % by wt	Temperature, Sections 1-12 °C	Speed rpm
	1	50 Kresoxim-methyl	50			30, 80, 90-90	200
25	2	50 Kresoxim-methyl	40	10		30, 80, 85-85	150
	3	50 Kresoxim-methyl	40	5	5, Tamol NH <sup>b)</sup>	30, 80, 85-85	150
30	4	50 Kresoxim-methyl	40	5	5, Wettol NT1 <sup>c)</sup>	30, 80, 85-85	150
	5	50 Kresoxim-methyl	40	5	5, Ufoxan 3A <sup>d)</sup>	30, 80, 85-85	150
35	6	50 Vinclozolin	50			30, 80, 90-90	200
	7	50 Vinclozolin	40	10		30, 80, 85-85	150
40	8	50 Vinclozolin	40	5	5, Tamol NH	30, 80, 85-85	150
	9	50 Vinclozolin	40	5	5, Wettol NT1	30, 80, 85-85	150
45							



## 16

Example No.	Active ingredient % by wt	Poly-ethyloxazoline % by wt	Lutensol AT 25a) % by wt	Addition % by wt	Temperature, Sections 1-12 °C	Speed rpm
5 10	50 Vinclozolin	40	5	5, Ufoxan 3A	30, 80, 85-85	150
					Sections 1-7	
10 11	20 bact. lipase	80			20, 50, 90, 90, 80, 80, 90	
12	10 pan-creatin	90			20, 50, 90, 80-80, 95	

- 15 a) nonionic surfactant based on ethoxylated fatty alcohols, alkylphenols, fatty amines and alkyl glucosides  
 b) condensate of naphthalenesulfonic acid and formaldehyde  
 c) sodium alkyl naphthalenesulfonate  
 d) ligninsulfonate

20

1.0 g of the 400-500 µm screen fractions of Examples 1-10 was in each case added to 1000 ml of deionized water. The resulting dispersion was stirred at 3 rpm for 5 minutes (IKA magnetic stirrer, RET-G, Janke & Kunkel GmbH, Staufen; 1 l glass vessel Ø 10 cm, T = 20°C). It was then filtered through a 160 µm wire screen. The residue on the screen as a % of the initial weight was:

	Example	Residue [%]
30	1	8.2
	2	2.1
	3	1.5
	4	2.8
	5	1.3
35	6	5.3
	7	0.8
	8	0.3
	9	0.5
	10	1.1

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The experiments demonstrate that the novel granules rapidly form a fine dispersion in water. They are therefore suitable for spray and distributor applications in agriculture.

45 Example 13

50% by weight of verapamil hydrochloride and 50% by weight of

## 17

polyethyloxazoline ( $M_w \sim 400,000$ ) were extruded under the conditions indicated below (Werner und Pfleiderer ZSK 30 twin screw extruder) and calendered to 500 mg forms.

5	Section 1	30°C
	Section 2	50°C
	Section 3	60°C
	Section 4	80°C
	Section 5	60°C
10	Die	60°C

The release after 1 hour was 100% (USP paddle method (pH change)).

## 15 Example 14

72% by weight of paracetamol and 28% by weight of polyethyloxazoline ( $M_w \sim 400,000$ ) were extruded under the conditions indicated below (Werner und Pfleiderer ZSK 30 twin screw extruder) and calendered to 500 mg forms.

25	Section 1	30°C
	Section 2	60°C
	Section 3	80°C
	Section 4	80°C
	Section 5	80°C
	Die	80°C

The release after 1 hour was 100% (USP paddle method (pH change)).

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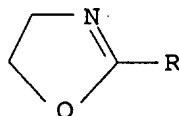
We claim:

1. A process for producing solid dosage forms by mixing at least one polymeric binder, where appropriate at least one active ingredient and, where appropriate, conventional additives to form a plastic mixture, and shaping, wherein homo- and/or copolymers of 2-substituted oxazolines are used as polymeric binder.

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2. A process as claimed in claim 1, wherein the oxazoline homo- or copolymers are composed of monomers of the formula

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where R is alkyl which may be interrupted by one or more oxygen atoms (between which there are at least 2 carbon atoms) or alkenyl, aryl, cycloalkyl or heterocyclyl, where R may have 1, 2 or 3 substituents which are selected, independently of one another, from alkyl, halogen, OH, alkoxy, acyl, acyloxy, COR<sup>1</sup>, SO<sub>2</sub>R<sup>1</sup>, amino, monoalkylamino, dialkylamino, nitro, aryl or heterocyclyl, where R<sup>1</sup> is OH, OC<sub>1</sub>-C<sub>6</sub>-alkyl, NH<sub>2</sub>, NHC<sub>1</sub>-C<sub>6</sub>-alkyl or N(C<sub>1</sub>-C<sub>6</sub>-alkyl)<sub>2</sub>, or R is also the abovementioned substituents which are, however, linked to the oxazoline ring via O, S, NR<sup>2</sup>, P(OR<sup>2</sup>)<sub>2</sub>, SiOR<sup>3</sup>, Si(R<sup>3</sup>)<sub>3</sub>, where R<sup>2</sup> is H or C<sub>1</sub>-C<sub>6</sub>-alkyl, and the R<sup>3</sup> radicals are, independently of one another, C<sub>1</sub>-C<sub>6</sub>-alkyl.

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3. A process as claimed in claim 2, wherein R is C<sub>1</sub>-C<sub>30</sub>-alkyl or C<sub>1</sub>-C<sub>30</sub>-hydroxyalkyl and, in particular, methyl, ethyl, hydroxyethyl, hydroxypropyl, stearyl, cetyl or palmityl.

35

4. A process as claimed in any of the preceding claims, wherein the formation of the plastic mixture takes place by mixing and/or melting the components in an extruder.

40

5. A process as claimed in any of claims 1 to 4 for producing dosage forms containing pharmaceutical active ingredients.

45

6. A process as claimed in any of claims 1 to 4 for producing plant treatment compositions, fungicides, herbicides or insecticides or mixtures thereof.

7. A process as claimed in any of claims 1 to 4 for producing

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animal food additives and supplements.

8. A process as claimed in any of claims 1 to 4 for producing human food supplements.

5

9. A solid dosage form obtainable by a process as claimed in any of claims 1 to 8.

10. A method for controlling fungal and insect pathogens of plants, and unwanted plant growth, which comprises treating the plants with a plant treatment composition obtainable as claimed in claim 6.

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